Biochemical research in psychiatry

Introduction

Over the last 10 years the Council has periodically 'reviewed the state of knowledge in the field of psychiatry' and has taken the initiative in promoting many promising lines of research, often on the advice of specially appointed expert committees. When therefore it was faced in 1968 with a series of problems in its units concerned with biochemical aspects of psychiatric disorders it was decided to consider the future of these units in relation to the organization and development of research in this particular area and to seek advice from experts in relevant fields. The Committee on Biochemical Research in Psychiatry (see p. iv) was accordingly set up, under the chairmanship of Professor D. A. K. Black, with the following terms of reference:

(i) to take evidence and to review the state of knowledge, as far as the Committee thinks necessary for its purpose, in the field of biochemical research in relation to psychiatric disorders;

(ii) to consider work in this field over the country as a

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whole, with special reference to (*a*) the need for the Council to have establishments working in this field, (*b*) the advisability of concentrating such establishments in suitable centres, and (*c*) whether or not such centres should be related to psychiatric hospitals, having regard to the fact that such institutions are usually separated from universities;

(iii) to consider what mechanisms, if any, are required to enable the Council to keep its policies in this field under continuous review.

The Committee held ten meetings. Three of these were combined with visits to the MRC Neuropsychiatry Unit at Carshalton, the MRC Brain Metabolism Unit in Edinburgh and the MRC Unit for Metabolic Studies in Psychiatry in Sheffield, together with workers in Leeds. The Committee also received written and oral evidence from 17 witnesses (see p. iv).

In this report the general situation is analysed first, with particular reference to the difficulties that have hampered the biochemical approach to psychiatric problems in the past and to recent developments that enhance the prospects for the future. The next section discusses four important areas of current biochemical research in relation to psychiatry—(i) the biogenic amines, (ii) carbohydrates, proteins and lipids, (iii) steroids, (iv) electrolytes—and this is followed by a short review of the mental disorders that have so far been the subject of biochemical investigation. The report concludes with a section devoted to recommendations on policy for the support of biochemical research in psychiatry; these cover the types of work that should receive continued or increased support, training and recruitment schemes and the location of units and groups.

The general problems

In our consideration of psychiatric problems we have consistently included both subnormality and mental illness.

Mental disorder implies an abnormal behaviour of the nervous system. Such disordered behaviour could be the result of previous interaction with the environment—that is, a learning phenomenon in the broadest sense. It could also arise from abnormalities in the functioning of some of the elements of the system. The two are interrelated: learning must involve a physical representation in the nervous system and changes in function may produce changes in behaviour. The Committee's terms of reference were confined to consideration of research involving investigation of chemical correlates of abnormal behaviour. 'Biochemical' has been interpreted as relating to those aspects of neurophysiology and neuropharmacology that are primarily concerned with observations of a chemical nature. In the course of the report it is sometimes necessary to distinguish techniques that investigate the activity or mechanisms of nervous tissue, for example neurochemical, neurophysiological, pathological and histochemical techniques, from those that are behavioural—for example psychological and sociological techniques. The former are termed 'neurobiological'.

The problems of mental illness have not in the past attracted a share of research effort commensurate with their importance in medicine and in society. This has been due primarily not to lack of interest or to lack of money but rather to a shortage of workers attracted to this field, and also perhaps to some aspects of the traditional care of the mentally ill or subnormal. The factors that may have impeded psychiatric research in general are not of course relevant to our terms of reference; but it is necessary to identify factors that may have hampered the biochemical approach to psychiatric problems. These can be classified as difficulties inherent in the subject-matter of this area of research, difficulties in recruiting suitably qualified research workers and difficulties arising out of the isolation of many of the hospitals catering for mental illness or subnormality.

Difficulties inherent in the subject-matter

One very obvious difficulty is the sheer complexity of the organization of the central nervous system, at whatever level this is studied—in terms of psychological function, chemical composition or electrical activity, let alone at the level of molecular biology or of the relation between patterns of neuronal activity and behaviour. The neurobiological basis of normal cerebral activity is far from established, in spite of much effort by skilled workers over many decades. Nevertheless, the neurobiological processes underlying abnormal cerebral activity must be deviations of those underlying normal cerebral activity; so any advance in our knowledge of neurobiology could prove relevant to psychiatric diseases, and should be encouraged for this reason as well as for its own intrinsic value.

While the chemistry of the normal brain is highly complex, it is at least accessible in experimental animals and through autopsy material in man; but in the mentally ill patient we have the further problem of inaccessibility of the relevant material. This inaccessibility is not absolute, but it does impose important restrictions on what can legitimately be done in the chemical study of mental illness. Chemical analysis of blood, or of tissues more easily accessible than the brain, is of uncertain relevance to chemical events within the brain. Moreover, neurochemistry can be presumed to be a dynamic subject, requiring kinetic studies as well as steady-state analysis. Furthermore, discrete mental functions are likely to depend on particular patterns of neuronal activity and certain classes of cells may have particular roles; it follows that relevant biochemical work may require the identification of cell populations of known function, rather than studies of the whole brain or of random samples of it. Details of the mechanisms involved may have to be sought in terms of subcellular constituents and their organization.

These are the obvious chemical difficulties; but others arise from the nature of mental illness, and our present knowledge of it. The indicants on which an adequate classification of mental disorder must be based are even harder to define than are the indicants of organic illness; it is therefore difficult to be certain that the syndrome or behaviour disturbance studied by one worker is either homogeneous within itself or identical with what is being studied under the same name elsewhere. This difficulty may be summarized as inadequate taxonomy.

Ideally, biochemical studies might be expected to contribute to an understanding of the aetiology of mental disorder, or to a sound pharmacological basis for therapeutics. In fact, much of the biochemical effort in the psychiatric field has been directed to the chemical phenomenology of mental illness or to the study of drugs empirically judged, often without the basis of a controlled trial, to be effective. These are useful and necessary studies, but they rarely lead to radical new knowledge at a fundamental level and may not be attractive to workers of the highest calibre. This brings us to our next category of difficulties.

Difficulties of recruitment

There is a shortage both of biochemists and of psychiatrists who are doing research in this field. While many more biochemists have been trained in recent years, the calls on them have also increased. Psychiatrists are inadequate in numbers. The consequent service load lessens the time available for investigation, and also may lead to premature award of consultant status—premature in the sense that it occurs after a training period too short to provide the opportunity for acquiring the techniques and outlook needed for research.

If a biochemist should be attracted to work in this field, in spite of competing claims for his skills, he may become discouraged either by the complexity and inaccessibility of his proposed material or at the other extreme by the relative superficiality of some of the work already published. He may also have difficulty in finding a psychiatrist with the time and the critical ability to characterise the problem adequately from the clinical point of view.

For his part, the psychiatrist anxious to take part in biochemical research must face the twofold difficulty of acquiring a degree of chemical understanding and of reaching a standard of critical diagnosis beyond what may be required for psychiatric practice.

Isolation

Mental hospitals have commonly in the past been large and isolated institutions with little or no access to centres in which biochemical studies were in progress. While it is of course perfectly practicable to install a chemical laboratory within the mental hospital, this is unlikely to command the diversity and sophistication of technical method and the facility of consultation with experts in other sciences that are characteristic of a biochemical 'centre of excellence'.

Isolation has also characterised the activities of some biochemists who have entered the field of research in mental illness. Discouraged by the complexities of psychiatric disorder, they have often withdrawn to investigate problems remote from, or peripheral to, clinical psychiatry.

The subject-matter of biochemical research in psychiatry often demands a multidisciplinary approach and this may be hampered, even within a medical school, by the orthodox departmental structure. Even when there is close geographical proximity between the neurologist, the psychiatrist and the psychologist, there still remains the more difficult task of creating conditions that allow the different specialists to understand fully each other's technology, methodology and intellectual approach. In effect what is needed is a multidisciplinary research team with some degree of continuity containing a certain number of people who are 'bilingual' or even 'multilingual'.

Changing circumstances

None of these difficulties is absolute. Much excellent work has been done in spite of them, and it might indeed be fairer to regard them as challenges. Moreover, there are some identifiable factors that make an intensified attack on psychiatric problems by biochemical means now seem opportune.

While the inherent problems set by the subject-matter remain, there are at least developments, within the broad areas of neurophysiology and molecular biology, of means of tackling them more effectively. These include both new ideas and new techniques, which need not be detailed here but can be exemplified. New ideas in the analysis of membrane transport and of subcellular organization may be mentioned; relevant techniques include tracer studies, histochemistry and histofluorescence, microinjection, and the powerful analytical techniques provided by the combination of gas-liquid chromatography and mass spectrometry.

The combination of new ideas and new techniques has generally shown itself a powerful attraction to research workers; and together with the inherent appeal of mental problems this may suffice to attract, and to retain, greater numbers of investigators with the necessary skills.

Psychiatry is also advancing, both in outlook and in organization. The development of drugs that inhibit violent behaviour, and the operation of the Mental Health Act, have made it possible to transfer patients from isolated mental hospitals to an environment where research can be prosecuted with the full backing of the resources of a teaching hospital or university. Such patients are to some extent selected, and there will always remain a place for investigation in the large mental hospitals and institutions caring for mental subnormality; but the more sophisticated and fundamental approaches may come to be concentrated in an environment more suited to the multidisciplinary approach on a wide front.

In relation to the difficulty of communication between the various relevant disciplines, the development of neuropharmacology has gone some way towards creating a bridging discipline. It would be difficult to overestimate the stimulus that has been given by the development of effective psychotropic drugs. On a severely practical level, these have made it possible to bring distracted patients into a research environment, and to enlist their effective co-operation; there is, of course, the difficulty that the very drug which makes the patient amenable does so by modifying his clinical state, and so possibly any underlying biochemical disturbance. More important still from the purely scientific aspect, these drugs have provided powerful tools of investigation, including the use of standard pharmacological techniques. They have also made it possible to work on animals in which disturbances of behaviour have been induced by psychotropic drugs. The progress which has already been made encourages the realistic hope that the origins of some forms of mental disorder may lie in a biochemical abnormality—a conclusion that would also be arrived at from consideration of the organic dementias. The development of psychopharmacology is important both as a bridge between clinician and biochemist and as an identifiable area of expanding research that is attractive to serious workers and also enjoys the interested support of pharmaceutical firms.

It is, in our view, opportune for the Council to encourage work on biochemistry in relation to mental disorders. This should be broadly based, ranging from studies of the chemical and physical organization of the brain to adequately designed clinical trials of agents whose mode of action can be chemically defined. It would clearly be neither desirable nor practicable in this report to attempt a review of the whole field, but in the next few pages a brief account is given of certain areas of current activity. This is arranged in terms of important classes of compounds—the biogenic amines, carbohydrates, proteins and lipids, steroids and electrolytes.

Biogenic amines

As far as is known, the biogenic amines of the brain are all localized in neurones, where they probably act as transmitter substances. The question of the function of the amines therefore becomes a question of the role played by these specific neurones. There is good evidence for the following functional relationships:

1 The integrity of at least some neurones containing

5-hydroxytryptamine (5-HT) is essential for sleep. No therapeutic benefit has yet been derived from this knowledge.

2 Destruction of a dopamine-containing nigrostriatal pathway leads to parkinsonism; therapy with dopa in this condition is based on this knowledge, although any improvement experienced by the patient and confirmed by clinical trial need not imply genuine substitution of a lost function. The biochemical disturbance underlying drug-induced parkinsonism in man has not been established, but one hypothesis suggests that phenothiazines and butyrophenones, when causing parkinsonism, block the dopamine receptors in the brain. Animal experiments have shown that these same drugs accelerate the turnover of dopamine in the brain; only very high doses lower the dopamine content of the tissue. Examination of human material is highly desirable to determine what biochemical changes are present in this type of parkinsonism.

3 There is little doubt that monoaminergic neurones influence mood, but the evidence has so far been entirely circumstantial. Overactivity of sympathetic centres, which are rich in adrenergic neurones, can be produced in animals by stress, and this is accompanied by a reduction in the noradrenaline content of the brain; sham rage elicited by electrical stimulation produces a similar reduction. Some effect on the turnover of the other monoamines has also been seen in stress. Though stress is linked with emotion, these observations do not answer the question whether the activity of some of the monoaminergic neurones is responsible for the emotion.

Production of depression by reserpine, which interferes with the binding mechanism of all amines, and the interaction of antidepressant drugs with amines, are the most compelling reasons for searching for a relation between mood and monoamines. The interpretation of the action of reserpine is made very difficult by the fact that it acts on the binding of all monoamines; furthermore, synthesis of amines is probably not interfered with by reserpine, and it remains a possibility that the amine loss—particularly that of 5-HT, which has the fastest synthesis—is not sufficiently severe to cause functional failure of the central monoaminergic neurones.

When inhibitors of monamine oxidase (MAO) were found to have an antidepressant action, few people doubted that their beneficial effect was due to the protection of amines from enzymatic destruction. When however, the tricyclic antidepressants, which lack ar inhibitory effect on MAO, were discovered, and when thei action was explained by their property of inhibiting amine uptake into nerves, the mode of action of the antidepressant inhibitors of MAO was reconsidered. It has been found that some of the MAO inhibitors, like the tricyclic drugs, prevented re-uptake of catecholamines, and that this property, rather than their potency as MAO inhibitors, ran parallel with therapeutic activity.

Even granted that there is a general connection between monoamines and affect, it is still uncertain which of the amines determines the improvement in mood; excess of dopamine, produced experimentally by injection of precursor, leads to arousal and great motor activity; excess of noradrenaline or 5-HT, similarly produced, causes sleep or stupor. Some of these effects may be produced because the amines accumulate at sites quite different from those they occupy normally and therefore also different from those they occupy when re-uptake is inhibited by antidepressant drugs; this may account for our inability hitherto to clarify the relation between individual monoamines and mood.

To test abnormalities in the activity of monoaminergic neurones in man is not at present practicable. Even cerebral amine metabolism can be studied only in a very limited way by examining metabolites in the cerebrospinal fluid. These are now being studied in manic-depressives in two centres in this country. A smaller concentration of 5-HIAA (5-hydroxyindole acetic acid, the main metabolite of 5-HT) has been found in the cerebrospinal fluid of manic-depressives than in that of other patients; during remission 5-HIAA concentrations slowly reverted to normal. The cause of this phenomenon is not clear and merits further investigation. A more searching analysis of the biochemical mode of action of beneficial drugs is still a most promising approach. In animal work greatest emphasis must be laid on the need for increasing the knowledge of the physiological actions of monoaminergic neurones.

Schizophrenia, at least in some of its forms, has been attributed by some to a metabolic error in amine metabolism. Catecholamines and indoles have been incriminated, but none of the theories has as yet been supported by indisputable evidence. Since therapeutic measures are usually palliative rather than curative, they are less likely to reveal the cause of the disease than in depressive illness, in which the normal state is restored, for a time at least. Though it is a fact that drugs useful in schizophrenia increase the turnover of dopamine in animals, this effect is more likely to be related to the motor side-effects of the drugs than to a role of dopaminergic neurones in the aetiology of schizophrenia.

Metabolism of carbohydrate, protein and lipid

Carbohydrate metabolism in the brain

The brain appears to be the only organ that is completely dependent on glucose both as a source of many metabolites such as glutamate and other non-essential amino acids and also as the supplier of energy for its continuous function. The brain has only very small amounts of glycogen, and other substances such as glycerol, maltose or lactate replace glucose only insofar as they are converted into glucose by the liver. This unique dependence on blood-carried glucose is to a large extent explained by the existence of permeability barriers. The entry of glucose appears to be dependent only to a relatively small extent on insulin, and in this way the brain differs from most other organs. The brain has apparently no glucokinase and its hexokinase is to a large extent bound to membranes. Recently it has been shown that there is in patients suffering from anxiety neurosis an increase in blood lactate. Clinical improvement was produced after infusion of calcium lactate. It is thus possible that in anxiety neurosis there is a change in intracellular calcium content, produced by an increase in systemic blood lactate. This intracellular level can be restored by supplying calcium ions.

Glycolysis and the tricarboxylic acid cycle occur in the brain mainly along conventional lines and it appears at present that particular emphasis on general carbohydrate metabolism in the central nervous system as such would not be justified. There will, however, always be special problems that may repay further attention.

Amino acids and proteins in the brain

When it enters the brain glucose is rapidly transformed, at least in part, into glutamate, γ-aminobutyrate and aspartate. These amino acids are present in all parts of the brain in high concentrations and there are good reasons for believing that they may be involved in the initiation or transmission of nervous impulses in the central nervous system. γ-Aminobutyrate is not present in any but very small concentrations in other organs. Another amino acid derivative, *N*-acetyl aspartate, is also found in significant amounts only in the nervous system and it is reasonable to ascribe to it a function peculiar to the generation or transmission of nervous impulses. It is also possible that local changes in concentrations of the amino acids mentioned may be important in nervous processes and that alterations in amounts of these substances in certain types of cells or in subcellular components may play a part in normal function or in disease.

Other specific amino acids on which attention might be concentrated are the aromatic compounds phenylalanine, tyrosine and tryptophan. These give rise to the biologically active amines adrenaline, noradrenaline and serotonin and others. It is not impossible that some amines not so far considered may be present in very small amounts in the brain and may have an important and specific function.

Many workers in different countries have used isotopically labelled amino acids in studies on the quantitative aspects of amino acid metabolism and protein turnover in the brain and have also arrived at certain conclusions about the turnover of protein. The results obtained with amino acids have revealed a great complexity, which is due to the multiplicity of compartments that communicate with one another at greatly varying rates. It appears that in principle this situation is not different from that existing elsewhere, for instance in the mitochrondria of the liver, but it is possible that the situation in the brain is especially complicated. It also seems that the brain contains proteins that are metabolically very stable, while others turn over at relatively fast rates. Meaningful results in this field can be obtained only if metabolic studies are done in parallel with morphological investigations, such as studies using electron microscopy and allied techniques.

Our knowledge of the proteins of the central nervous system (CNS) is still remarkably incomplete. Proteolipids, first described by Folch-Pi in 1951, are complexes composed of protein and lipid, are soluble in methanol-chloroform and can be separated into several fractions. It is uncertain whether they are uniquely characteristic of the CNS or whether they have a specific function in nervous activity.

Other proteins have been isolated from the CNS, such as neurokeratins, which are distinguished by poor solubility in a variety of solvents. Recently some basic proteins of low molecular weight have been isolated from brain, one of which at least acts as an antigen in experimental encephalitis. A more comprehensive study of the CNS proteins, using modern methods, is highly desirable.

Lipid metabolism in the brain

The central nervous system contains a relatively large amount of lipid matter and the variety of structures of lipid type is possibly greater in the brain than in any other organ. Lipids normally supply little or no oxidative energy in the brain and this is possibly the reason why this organ contains such small amounts of triglycerides. On the other hand there is an abundance of cholesterol, phospholipids such as phosphatidylcholine, phosphatidylserine, plasmalogen, sphingomyelins, phosphatidylinositols, sulphated lipids and glycolipids such as gangliosides. The fatty acids present include, apart from the ubiquitous substances such as palmitic, oleic and linoleic acid, some very highly unsaturated fatty acids and some unusual γ-hydroxy fatty acids. Whether the last two groups of substances have a special function in the brain is uncertain.

A large part of the lipid is present in the various membranous structures such as mitochondria or synaptosomes, and these lipids may be considered to have a 'structural' function in the sense that they separate the structure of the organelle of which they form a part from the mainly aqueous environment of the cytoplasm. Cells in the central nervous system, like other cells in the body, represent a three-dimensional mosaic in which volume elements, which are aqueous, alternate with others that have a low dielectric constant and in extreme cases may actually resemble solutions of hydrocarbons. Lipids must play an essential part in bringing about this organized heterogeneity.

It is likely, however, that lipids are also closely connected with the transport of ions and electrons and the transmission of nervous impulses across boundaries. The great variety of structural features among the lipids may indicate a specific local requirement within the cell and may allow for special functions of nervous activity or specificities of neuronal messages.

Myelin, which has long been known as a histological entity, can be prepared in bulk and the metabolic stability of its components has been investigated. It consists of protein, cholesterol and a variety of phospholipids, cerebrosides and sulphates. Myelin is characteristic of the maturing or mature peripheral and central nervous system. Another subcellular structure specific to the central nervous system is the synaptosome, which is a complex structure morphologically; this also can be prepared in bulk.

Steroid hormones

Psychological changes have been known for many years to occur in patients with abnormalities of corticosteroid secretion and this has led many workers to investigate adrenal function in patients with mental disorders.

A complete assessment of hypothalamo–pituitary–adrenal function involves the following measurements: (i) secretion rate of cortisol; (ii) concentration of cortisol in blood at the peak of the diurnal range, usually at 8-9 a.m.; (iii) assessment of the diurnal rhythm by serial sampling of blood at intervals of hours throughout the day and night; (iv) response of the hypothalamo–pituitary–adrenal system to stimulation and suppression tests; and preferably also (v) excretion of corticosteroid metabolites in urine; and (vi) measurement of the protein binding of cortisol in plasma, the unbound cortisol being the active fraction.

Although many papers have been published on adrenal function in mental disease, they have seldom included the full range of tests as listed above. Moreover, the patients studied have commonly been few in number, have not been drawn from a uniform category of disease and have not been adequately graded in terms of severity. Since the range of normal variation of the indices of adrenal function is very considerable, results in patients with only mild degrees of mental disturbance may appear to be normal even if they are in fact abnormal for the particular patient, and it may not always be possible to observe the same patient in different phases of his illness and after recovery. Since most patients with mental illness now receive drugs, changes in steroid levels during recovery may represent a direct effect of the drug rather than a regression of the disease process. The effects on steroid metabolism of some of the drugs used have not yet been fully studied; for example, when electroconvulsive therapy has been used in treatment, the effect of anaesthetic or sedative agents on steroid metabolism has not always been considered. In the same way, the disturbance of the diurnal rhythm of steroid metabolism simply by a change of environment (for example admission to hospital) has to be allowed for. The difficulties of obtaining adequately matched controls have proved even greater in studies of mental disorder than in other clinical work. Even when due allowances have been made for all these difficulties and methodological inadequacies, a change in pituitary–adrenal function seems clearly established in depression.

Increased adrenal activity has been demonstrated by many workers in a high proportion of patients with endogenous depression. Increased excretion of cortisol metabolites in urine, an increased secretion rate of cortisol and increased concentrations of corticosteroids in plasma have all been found, with levels returning to normal after treatment (drugs or electroconvulsive therapy) when clinical improvement is evident. A connection between high values of steroids in the morning and the early morning wakefulness and the morning exacerbation of mood found in depression has been postulated. A diurnal rhythm is usually present, but disturbance in the timing of the cycle has been observed. However, similar disturbance has been found in the diurnal rhythm of plasma corticosteroids in control subjects and may be due to the effect of hospitalization, particularly during the period immediately after admission. Changes in the time of the morning plasma cortisol maximum could lead to false conclusions when measurement is made at a single fixed time of day.

Lack of suppression of pituitary–adrenal function by dexamethasone and lack of response to insulin-induced hypoglycaemia have been demonstrated in a high proportion of depressed subjects, and a significant correlation between the responses to these two tests was also shown. Normal responses were usually obtained on recovery.

These findings have been variously interpreted. High levels of corticosteroids have been regarded by some as a cause of the depression, while others have regarded them as a consequence of the emotional stress of mental illness, acting as a stimulus to pituitary–adrenal activity. A third view is that a primary lesion, possibly in the hypothalamus, produces both the mental illness and the pituitary–adrenal stimulation.

In schizophrenia and non-depressive psychoses, plasma cortisol is usually in the normal range but is sometimes raised, possibly because of associated or secondary depression.

Until recently, research into the role of gonadal steroids in mental illness in women has been hampered by the insensitivity of available methods. The introduction of gas chromatography, double-isotope labelling and competitive protein-binding methods for gonadal steroids opens up the possibility of estimating progesterone, testosterone and oestrogens with greater accuracy and on a larger scale. It is already known that the excretion of dehydroepiandrosterone increases during recovery from depression, and further studies of gonadal steroids may produce additional information on this and other conditions.

Electrolyte metabolism

The central nervous system, like the rest of the body, is permeated by electrolytes, and neural activity is characterized at the physiochemical level by changes in electrical potential brought about by ionic shifts. It is not surprising that attention has been paid by inquiring psychiatrists to electrolyte metabolism. Interest has been stimulated in the past few years by a range of observations on the 'electrolyte household' in psychiatric disorders, and by the fact that lithium salts have a beneficial therapeutic effect on some, but by no means all, patients with manic-depressive psychosis. These constitute two separate lines of evidence that electrolyte disturbances, whether causal or consequential, arise in the context of psychiatric disorder.

General electrolyte changes

Retention of sodium has been reported in the depressive phase of manic–depressive psychosis, in depressive episodes in normal people, in rapidly fluctuating cyclothymia and in premenstrual tension. Estimates of the degree of retention based on balance studies and on isotope dilution methods have not been wholly consistent and consequently alteration in the internal distribution of sodium has been postulated. An increase in 'residual sodium' has been described in depression, in a study that failed to show the increase in total exchangeable sodium found by other workers. When total sodium balance is affected comparable retention of water has been observed, suggesting that some of the change is in extracellular fluid; but when the latter has been measured by isotope dilution, it has generally been found to be reduced in the depressive phase. Intracellular potassium has been described as reduced in depressive illness, but the calculation is based on an isotope estimate of extracellular fluid. Other changes described in depressive illness are a decreased amplitude of the diurnal rhythm in electrolyte excretion and a diminished rate of sodium transport in the salivary gland. Studies are lacking on calcium, magnesium, and acid-base status in psychiatric illness.

It is not easy to assess the significance of the studies summarized in the preceding paragraph. There are divergent findings between different groups of workers; the limitations of isotope dilution methods in psychiatric patients may not have been given full weight, and the cumulative error of derived quantities such as 'residual sodium' is hard to assess. There is a clear need for a more critical study of the sodium balance in depressive illness, using not only isotope dilution methods but also balance studies and perhaps even muscle biopsy in the same group of patients.

Even given a consensus of results obtained by sound methods, there are the following conceptual difficulties in the way of ascribing a causal role to this type of electrolyte change:

1 Patients with cardiac failure or hepatic cirrhosis have much larger distortions of the electrolyte household than any described in depressed patients; yet these are not associated with any consistent disturbance of behaviour. There is indeed anecdotal evidence of asthenia in potassium depletion, excitability in over-hydration, and anomalies of behaviour in alkalosis; but there is generally the complication of the causal illness, and no professional analysis of behaviour seems to have been made in human experimental electrolyte depletions.

2 Although it has been stated that similar alterations in sodium and potassium in the brain tissue would greatly modify the excitability of neurones, there is no direct evidence on the content or distribution of sodium and potassium in brain, or indeed in any tissue from psychiatric patients. Even if the situation in other tissues were precisely known, extrapolation to neural tissue would be hazardous, because of the slow penetration of isotopes—for example ^{42}K—into the brain, and the much smaller proportion of extracellular fluid in cerebral tissue.

The lithium effect

Although lithium salts were first introduced for the treatment of 'psychotic excitement' in 1949, they have not been extensively used until much more recently. They appear to be of value in controlling manic excitement; but while some reports claim that they also alleviate depression in some patients, others claim at best an adjuvant action with the tricyclic or MAO-inhibiting antidepressants. One double-blind trial suggested a 'mild antidepressant action'. Suppression of short-cycle cyclothymia by lithium salts has been convincingly reported. There is a good deal of evidence that lithium is an effective drug in the treatment of mania, though possibly no more so than the phenothiazines, and some evidence that it may help some patients in the depressive phase as well. The status of lithium as a therapeutic agent may be more firmly defined when the results of further controlled trials are available.

Assuming that lithium is effective, at least in mania, does its effectiveness have a bearing on the aetiology of manic–depressive disorders? The administration of lithium salts is followed by an increase in sodium excretion, which is more striking in normal people than in manic–depressive patients. There are decreases in serum sodium and serum calcium levels. The increase in serum lithium is greater in normal individuals than in patients. The retention of lithium itself is clearly important; this is reported as greater in acutely manic patients than in 'normothymic' patients, and in patients who show a therapeutic response than in those who fail to do so. Lithium administration increases the destruction of noradrenaline in the brain, inhibits the release of noradrenaline and serotonin on electrical stimulation of brain slices, increases the uptake of noradrenaline by synaptosomes and may inhibit release of synaptic neurotransmitters.

The currently available evidence is clearly inadequate to decide whether lithium has a direct action on neural tissue or whether it acts indirectly, either by changing the concentration or distribution of other electrolytes or by its effect on biogenic amines.

Future work

While it would be uncritical to suggest that the key to understanding any psychiatric disorder should lie in electrolyte studies, these are worth pursuing on the following lines:

1 The phenomenology of the electrolyte household in patients with affective disorders should be studied further, by more than one method and in more than one centre, and with equally critical characterization of the psychiatric disorder.

2 The short-cycle manic–depressive syndrome is a specially good model for such studies, in spite of its rarity.

3 The lithium effect is worthy of intensive study at two levels—the validation or otherwise of the therapeutic effect of lithium, which again demands critical psychiatric taxonomy and properly designed trials, and pharmacological studies down to the molecular level, including also further work on the distribution and excretion of administered lithium.

In the preceding section we have done little more than exemplify the possible roles of selected classes of chemical compounds in mental illness. The subject can clearly be looked at in another way, by taking the various recognized types of mental illness and recounting what has been found in them by chemical investigation; we would draw attention to a valuable report of a WHO Scientific Group* that reviews the subject in this way. It would be quite

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*World Health Organisation (1969) *Technical Report Series* No. 427. Geneva, WHO redundant in the present report to attempt anything on the same scale, but a note on the problem from the clinical aspect is given by way of summary.

Mental disorders and biochemical investigation

Great advances have been made in the understanding of those rare but clear-cut and important types of mental subnormality in which specific biochemical defects of genetic origin have been described. Phenylketonuria is the most obvious and best known example, and is particularly important in that a rational treatment of dietary restriction is being applied, though the long-term value of the treatment still requires proof. Increasing attention is also being paid to possible nutritional disorders leading to disturbances of growth *in utero* and in early life, especially at those stages of development when growth of the central nervous system is at its most active. The biochemical aspects of the various chromosomal syndromes described in recent years still require investigation. The biochemical correlates of other known brain disorders are still little studied, though neuropathologists are rapidly moving away from morphological to biochemical studies, especially in the so-called storage diseases and in degenerative conditions of old age. A good deal of work is also done on various forms of epilepsy, though the psychiatric effects of this type of disorder are more likely to be understood through neurophysiological than biochemical techniques.

Although numerous diseases of the liver, cardiovascular system, respiratory system and indeed almost any organ of the body can produce mental changes, it has long been thought that the resulting psychiatric states (which are mainly some variety of confusion or dementia) are not on the whole specific to the underlying medical disorder. Little light is therefore thrown by their study on anything other than the vulnerability of the mechanisms underlying consciousness to a variety of biochemical disorders. In contrast, the fields of psychopharmacology and neuropharmacology (if they can be separated) are rapidly expanding, though basic knowledge of the mode of action of the drugs still lags behind their empirical use in the treatment of mental disorders.

The above remarks refer to conditions in which there are known biochemical disturbances of a gross or static character such as an enzyme defect or an excess or absence of certain crucial metabolites. The success of biochemical investigation is much less certain in those psychiatric disorders where no such gross disturbance has yet been found. The aetiology of these conditions (which constitute the great majority of psychiatric disorders) has almost always been regarded as a multifactorial complex of constantly interacting constitutional and environmental influences. The common protean and long-lasting disorders of thinking, affect, volition and behaviour that are lumped together as schizophrenia have been the object of intense interest for years. It is safe to say that whenever a method has been described for detecting a new metabolite in the body a paper on its occurrence in schizophrenia will appear somewhere within a few months. Much of this work may be described as biochemical anecdotalism and as such may have little value. More experienced workers realise the need for turnover studies and for serial sampling rather than static biochemistry if any biochemical changes accompanying the variation in the clinical state of the schizophrenic patient are to be revealed. It is not, of course, certain that the currently accepted multifactorial model for schizophrenia is in fact the correct one, and the possibility of a critical biochemical anomaly, still to be discovered, cannot be entirely ruled out.

Schizophrenia was particularly intensively studied in the 1940's and 1950's; in recent years interest has shifted more to the affective disorders, especially depression. This is partly because the cyclic nature of most depressive illnesses, as opposed to the less predictable and aperiodic nature of schizophrenia, appears to make serial studies of biochemical changes correlating with the clinical change easier to carry out. The striking success of anti-depressant drugs has also given a tremendous impetus to research in this field. These studies are important even though they do not yet throw light on whether the biochemical changes are cause or effect of the mental state, or whether both are related to some more fundamental underlying instability.

Much the same considerations have applied to the study of anxiety and many so-called psychosomatic disorders. It is perhaps surprising that so little has been done on the premenstrual disorders, which are so common, occur with conveniently short periodicity and are obviously associated with cyclical endocrine changes.

The basic sciences underlying psychiatry are perhaps at last coming more into balance, so that fruitful collaboration can soon be expected between the neurobiologist and the behaviourist. Learning, appetites (especially the complexities of sexual behaviour), sleep and arousal are just a few of the fields in which an understanding of normal neurobiology will contribute fundamentally to our knowledge of frank psychiatric disorder.

Recommendations

It would, of course, be quite unrealistic to suppose that the answer to all the major problems of psychiatry could come from biochemistry, or even the broader field of neurobiology; this would be to neglect the massive role of psychodynamic and social factors. Nevertheless, biochemical studies within the broad framework of neurobiology offer a tangible approach to important aspects of mental functioning, as is shown by the illumination cast on our notions of human and animal behaviour by advances in psychopharmacology. Moreover, physical and chemical methods of treatment are often effective, and presumably the effects are achieved by organic means; study of such organic mechanisms clearly has to be carried out by the established methods of neurobiology, and on the analogy of clinical medicine can be expected to shed light on the aetiology and pathogenesis of disease. Furthermore, our understanding of the mechanisms of the nervous system and hence of the processes underlying behaviour derives largely from neurobiology. The development and use of methods for the observation of correlates between abnormal behaviour and underlying changes in the nervous system is therefore an important, if long-term, approach to the understanding of behavioural disorder.

Our first and major recommendation must therefore be that *the Council should encourage the neurobiological approach to psychiatric problems, both broadly and in depth, and on a substantial scale.* We have been impressed by the evidence given us of the value of a multidisciplinary approach, both when this is concentrated on psychopharmacology, as in the MRC Brain Metabolism Unit, and when it aims at covering a wider field, as in the MRC Neuropsychiatry Unit. We therefore recommend that *the multidisciplinary attack on neurobiological problems should be supported.*

We have taken much evidence, in the light of which we have considered the most appropriate type of site for research in the neuropsychiatric field. One view is that the essential requisite is access to a large number of patients, from whom a selection of those suited for study can be made; the opposite view is that a unit should be located on a university site, in proximity both to basic departments and to a university department of psychiatry. It is no longer the policy of the Health Departments to retain large mental hospitals (with their disadvantages of isolation—see p.6) and they favour instead the establishment of psychiatric units attached to district general hospitals. Attention should thus be paid to alternative methods of obtaining large populations of patients, for example by means of psychiatric registers of the type maintained in Camberwell and Aberdeen. Work that depends on the study of large numbers of patients by simple observational techniques, and could well be sited at present in a complex of large mental hospitals, will call for a new type of organization. However, for the large-scale multidisciplinary study in depth of problems arising out of psychiatry, we are convinced that *the balance of advantage lies strongly with a university setting*, for the following reasons:

(1) From the purely scientific point of view, there is the overwhelming advantage of ready contact with the full range of both clinical and basic disciplines.

(2) A strong academic department of psychiatry may well attract selected patients from a wide area.

(3) Patients can be studied in depth, and carefully characterized, from the purely clinical aspect. For many studies, clinical as well as scientific, a small number of thoroughly studied patients are more appropriate than a much larger number who have been investigated more superficially.

(4) The development of population surveys could be

facilitated by contact with a department of community medicine.

Types of work to be encouraged

The Committee has had to steer a middle course between suggesting specific lines of detailed investigation and resting content with appealing for multidisciplinary research—as it has just done—without giving any indication of which disciplines it has in mind. A problem of this complexity demands more than one approach, and we envisage three main types of study:

(1) Basic studies using neurobiological techniques, directed towards increasing our knowledge of the functions of different components of the brain.

(2) At the other extreme, straightforward observational work on recognized psychiatric disorders aimed at elucidating their natural history and their biological and biochemical correlates.

(3) Studies of a 'bridging' character, including neuropharmacology and in particular the use of animal models, and macroscopic, microscopic and ultramicroscopic neuropathology.

Of these types of study, the first (basic neurobiology) is being actively pursued in many university departments, particularly of physiology, as well as in MRC establishments; similarly the second (observational studies in psychiatry) is attracting a considerable amount of effort—some of it, particularly in the field of social psychiatry, with Council support. There is, however, great scope for development of the 'bridging' type of research, and it is perhaps particularly here that the Council has already played a role with units that span the gap between clinical studies and basic work. It could play a greater role in the future by supporting psychopharmacology and by expanding the type of activity exemplified by the existing

MRC Brain Metabolism, Neuropsychiatry, Metabolic Studies in Psychiatry, Neuroendocrinology and Neuropharmacology Units.

The three headings given above are very general; it would not be possible to give a comprehensive account of the many suggestions for further work that we have received, but it may be worth giving a few examples of possible developments in each of these three areas.

(1) *Basic studies* Possible directions in which these might be encouraged to expand, with reason to hope that some of the results might be relevant to psychiatric problems, include the following:

(*a*) The application of refined methods of both ultramicroscopic scrutiny and biochemical microanalysis to subcellular components of neural tissue, for example organelles, synaptosomes and cell membranes.

(*b*) The development for this purpose of new methods and also the application to neural problems of methods already established in other fields, for example microtechniques for studying distribution, the Lowry histochemical technique for differentiating nicotinamide adenine dinucleotide in its oxidised and reduced forms and an extended use of gas-liquid chromatography/mass spectrometry and nuclear magnetic resonance.

(*c*) Study of the critical periods of brain maturation, with particular reference to the effect of giving thyroxin or steroids and also in terms of the chemical anatomy of the brain itself.

d) Further study of the distribution of biogenic amines and their role as neurotransmitters, and the application of isotopic techniques to these problems.

(*e*) Studies of cerebral constituents such as glutamine and γ-aminobutyric acid in spontaneous and induced convulsions.

(*f*) Genetic differences, for example differences between 'strains' of the same species, in cerebral composition, in the pharmacokinetics of psychotropic drugs and in behaviour patterns.

(*g*) Study of simple brains in which it might be possible to isolate neuronal and glial components.

(*h*) Studies on cell cultures.

(2) *Observational studies* Fundamental to advances in this area is an insistence on the highest available standards of methodology and data processing, whether the techniques used are clinical, epidemiological, biochemical, physiological or histological. Specific areas for relevant study may include:

(*a*) The application of detailed psychiatric analysis to organic disorders that alter mental function—for example metabolic disorders, (both congenital, such as phenylketonuria, and acquired, such as acute intermittent porphyria), epilepsy, parkinsonism and the toxic dementias. Much would be gained if the psychiatric assessment were made on several occasions, on each of which possibly relevant variables, for example steroid levels in blood, were assayed by reliable methods.

(*b*) The effect of psychotropic drugs on those variations in mood that lie within the physiological range and have the convenience of predictability—for example premenstrual tension and the effects of oral contraceptives—and on the depression that can follow organic illnesses such as influenza and hepatitis.

(*c*) Study of the behavioural changes resulting from localized lesions, particularly those that can be accurately defined at autopsy or in some instances by biopsy undertaken in the course of a necessary intracranial operation.

(*d*) Further study of the changes in body fluid and electrolytes in manic–depressive states, particularly those with short and predictable cycles. With proper ethical safeguards muscle biopsy could be a useful addition to the methods of study.

(*e*) *Controlled trials* The disciplines of the controlled trial should be more widely applied in psychiatric disorders.

(*f*) *Data processing* The advent of the computer has made it possible to undertake the analysis of clinical, psychological, sociological and neurobiological data on a scale that could not formerly be contemplated. This will, for example, permit the revision of accepted psychiatric syndromes and possibly the delineation of new categories of disease, and thus help to elucidate their neurobiological correlates.

(3) '*Bridging*' *studies* We have been impressed by the importance of psychopharmacology as a 'bridging' discipline between basic neurobiology and purely clinical studies. This is already an active field, but there is still a need for further work in research organizations not primarily directed to the production and testing of psychotropic agents. Another bridging discipline is chemical pathology; much remains to be done in the detection of the biochemical correlates of psychiatric disorders by means of reliable methods. The following are examples of possible lines of work:

(*a*) Studies of the blood levels of drugs that either alleviate or produce disturbed behaviour, and of their absorption, distribution and excretion, using tracer techniques as well as chemical estimation.

(*b*) The use as models of animals whose behaviour has been modified, for example by psychotropic drugs, by localized, stereotactically defined lesions, by psychological techniques or by methods deriving from ethology.

(*c*) The distribution and action of lithium salts in animals.

The division of 'types of work to be encouraged' into three broad categories is of course somewhat arbitrary, and indeed it may well be that major progress can be made only by those who are prepared to cross such arbitrary divisions and occupy the territory between the conventionally established disciplines. The difficulty in selecting work for Council support may well lie in deciding whether new and adventurous ideas are relevant to actual problems and whether the proposed methods of study are sufficiently rigorous. Real progress will not come from work that does not satisfy the criteria of excellence to be expected in other branches of medical research, and the difficulties in the subject-matter can be resolved only by work that satisfies strict criteria. It follows that a major prerequisite of success is that workers of quality should be attracted into the field in greater numbers.

Recruitment and career structure

Recruitment and career structure are not separate problems; if a field of research is to attract the best recruits, it must not only be inherently interesting and challenging but must also offer to the potential entrant adequate facilities for training and a long-term career structure, with reasonable opportunities of reaching a responsible senior appointment. The responsibility for providing such a career structure rests in part with the universities and Health Departments, and the role of the Council may lie in providing support at critical points—for example in the training period—and in the creation of established posts for workers with some experience of this type of research, who may be tempted to abandon work on the biochemical aspects of psychiatry for a career post of another kind. Jointly with the universities, the Council might consider the provision of funds for the establishment of appointments up to consultant level between university biochemical and psychiatric departments for psychiatrists and medical and non-medical biochemists, and also provide certain other facilities when necessary. The Health Departments might be consulted about the ways in which research opportunities could be provided for those engaged in psychiatric practice.

In our interviews with witnesses we have made training and career structure the subject of particular inquiry, and these are among the suggestions that we have received:

1. For *medical graduates*, opportunities to engage in research or relevant training with support from the Council are available at a number of stages—intercalated honours degrees, junior research fellowships, clinical research fellowships and grant support. These facilities should be more widely known to heads of academic departments of psychiatry, who are in a position to identify students and graduates with a potential contribution to make.
2. For *science graduates*, some priority should be given to neurobiological studies relevant to psychiatry in the selection for training awards; at the junior level these are awarded to departments rather than individual students, but departments with an interest in training scientific workers in this area might be identified. At a more senior level, encouragement can be given initially by grant support and later by career appointments.
3. Entry to the field will be stimulated by the formation of a larger number of active centres. These are likely to be more attractive both to clinicians and to other scientists if they are part of a university complex, with its library facilities and opportunities for contact with other workers in various disciplines.

None of these measures compensates for a lack of gifted individuals dedicated to this important area of research. Such individuals should be sought out and given the maximum support appropriate to their seniority, for example by the formation of new groups or units. To permit the participation of an adequate range of disciplines a number of units would need to be built up to an appropriate size.

Summary of recommendations

1. The Council should actively encourage and give increased support to the neurobiological approach to problems related to mental illness and subnormality.
2. Multidisciplinary studies should be supported, in particular those which might serve to bridge the area between basic neurobiology and observational studies on patients.
3. The optimum setting for large multidisciplinary teams working on psychiatric problems is in a university with strong departments both of the sciences basic to medicine and of academic psychiatry, psychology and sociology.
4. A number of possible areas for further work have been identified, but MRC support for them should be contingent on scientific merit, sound methodology and a reasonable likelihood of their ultimate relevance to psychiatric problems.
5. In order to attract more workers into this important field it is necessary to create a recognisable career structure. The Council should contribute to a co-ordinated scheme of training posts and career posts, including appropriate senior posts with security of tenure.
6. The Council should give consideration to the strengthening of existing units and to the formation of new teams, some of which might be substantial in size and multidisciplinary in character.

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Medical Research Council

Biochemical research in psychiatry: survey and proposals

Report by a Council Committee

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The Medical Research Council has accepted this report as the basis for its policy in the field of biochemical research in psychiatry. If resources are available, the recommendations will be implemented wherever favourable opportunities occur.

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Members of the Committee on Biochemical Research in Psychiatry

Professor D. A. K. Black (*Chairman*)
Professor C. H. Gray
Professor A. Neuberger
Professor D. A. Pond
Professor M. Roth
Professor T. Symington
Dr Marthe Vogt
Sir Brian Windeyer

Expert witnesses who gave evidence to the Committee

Dr H. F. Bradford
Professor P. B. Bradley
Professor A. S. V. Burgen
Dr J. A. N. Corsellis
Professor J. N. Cumings
Dr H. Davson
Professor C. E. Dent
Professor E. J. Field
Dr J. Gibbons
Professor G. W. Harris
Professor Sir Denis Hill
Dr M. H. Lader
Professor H. McIlwain
Professor A. Neuberger
Professor W. D. M. Paton
Dr S. P. R. Rose
Dr Marthe Vogt